

CYP2D6 and CYP2C19 Polymorphisms as Predictors of Antidepressant Response

Clinical Applications of CYP2D6 and CYP2C19 Pharmacogenomics

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Abstract

Precision medicine aims to tailor therapeutic interventions to individual patients by integrating genetic, environmental, and lifestyle factors. In the context of Major Depressive Disorder (MDD), traditional antidepressant prescribing is hindered by variable drug response and a high prevalence of treatment resistance. Pharmacogenomic (PGx) testing, particularly for the cytochrome P450 enzymes *CYP2D6* and *CYP2C19*, offers a clinically actionable approach to guide drug selection and dosing. This review synthesizes current evidence on the role of *CYP2D6* and *CYP2C19* polymorphisms in antidepressant metabolism, the resulting metabolic phenotypes, and their implications for efficacy and adverse drug reactions. PGx-guided therapy has been shown to improve response and remission rates compared to conventional treatment, while reducing the risks of under- or overexposure. Challenges to widespread implementation include cost, clinician training, and multi-gene interpretation complexity, though integration into electronic health records and emerging polygenic risk scores may facilitate broader adoption. Overall, PGx testing represents a validated, practical tool to individualize antidepressant therapy, offering a pathway toward more effective and safer treatment strategies for MDD.

Keywords: Pharmacogenomics, CYP2D6, CYP2C19, Antidepressants, Major Depressive Disorder (MDD), Precision Medicine, Personalized Therapy, Treatment-Resistant Depression (TRD), Drug Metabolism, Genetic Polymorphism

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1. Introduction

1.1. Context and Background

Genetics plays a foundational role in modern medicine by explaining why individuals differ in their susceptibility to disease and in their responses to therapeutic interventions. Together with environmental exposures and lifestyle influences, these genetic differences shape the considerable variability seen in drug effectiveness and safety. Precision medicine is an emerging approach that aims to optimize patient care by accounting for individual variability rather than applying uniform, standardized treatment strategies. It incorporates multiple sources of variation, including genetic makeup, environmental exposures, and lifestyle components, to support more accurate diagnoses

and more precisely targeted therapies. By moving beyond the traditional one-size-fits-all model, precision medicine seeks to improve overall treatment outcomes and reduce the likelihood of therapeutic failure [1]. Pharmacogenetics, a central component of precision medicine, focuses on identifying genetic variants that shape drug response [2].

Treating Major Depressive Disorder (MDD) remains challenging because initial antidepressant response rates are low and vary widely among patients. MDD is often under-diagnosed, complicated by somatic symptoms, and commonly co-occurs with chronic medical conditions, delaying accurate treatment. Even with proper diagnosis, many patients do not respond to first-line therapy. Large clinical datasets, such as STAR*D, show that roughly 30% of patients do not achieve remission even after several antidepressant trials, underscoring the presence of a substantial treatment-resistant subgroup [3]. These outcomes reflect the biological and social variability within MDD, making standardized, trial-and-error prescribing inadequate. This gap underscores the need for more individualized strategies such as pharmacogenomic (PGx)-guided therapy to optimize initial drug selection and reduce repeated treatment failures.

1.2. Scope and Thesis

This review examines the clinical role of PGx in guiding antidepressant prescribing, with a particular emphasis on

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its potential to improve treatment selection and patient outcomes. The central argument of this paper is that PGx testing of key Cytochrome P450 enzymes, particularly *CYP2D6* and *CYP2C19*, can significantly enhance the prediction of drug response and optimize therapeutic outcomes for individuals undergoing antidepressant therapy.

2. Materials & Methods

2.1. Literature Search Strategy

To gather the materials for this review, our team conducted a literature search across several major scientific databases, including PubMed, Google Scholar, and Web of Science. We used a range of search terms related to the topic, such as “pharmacogenomics and antidepressants,” “*CYP2D6/CYP2C19* polymorphisms,” “*CYP2D6* and *CYP2C19* dose adjustments,” “Major Depressive Disorder (MDD),” “drug metabolism genetics,” “precision medicine,” “CPIC guidelines,” “DPWG guidelines,” “tricyclic antidepressants,” and “SSRIs.” These articles were selected based on the following criteria: peer-reviewed publications, clinical guidelines, and review papers published between 2000 and 2025, with a clear focus on PGx and antidepressant therapy. Non-peer-reviewed sources, including conference abstracts and opinion pieces, were excluded to ensure that only reliable and clinically relevant evidence informed the review.

2.2. Data Extraction and Synthesis

We extracted and synthesized data from the selected sources, focusing on key PGx elements such as the specific genes involved (e.g., *CYP2D6*, *CYP2C19*), the corresponding antidepressant drug classes (e.g., Selective Serotonin Reuptake Inhibitors (SSRIs), Tricyclic Antidepressants (TCAs)), and the predicted metabolic phenotypes including ultrarapid, normal, intermediate, and poor metabolizers. Clinical recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) were also collected, along with comparative findings evaluating treatment-as-usual versus PGx-guided antidepressant therapy in patients with MDD.

After extraction, the information was systematically synthesized and organized into three central thematic categories: Genetics in Etiology and Diagnosis, Applications in Therapy, and Clinical Challenges and Future Directions. This structure provides a coherent framework that guides the development of the Discussion section and enables clear integration of the evidence across studies.

3. Discussion

3.1. Genetics in Etiology and Diagnosis

3.1.1. Introduction to Pharmacogenomics and Genetic Variation

The most common form of DNA variation among individuals is the single-nucleotide polymorphism (SNP). SNPs are fundamentally a substitution of a single nucleotide that occurs at a specific position in the genome. These common variants occur approximately once in every 1 000 nucleotides on average or, more broadly, every 300 – 2 000 base pairs, meaning a person’s genome contains roughly 4 – 5 million SNPs [4]. SNPs are responsible for conferring genomic diversity and generating phenotypic differences among individuals. Although most SNPs do not affect health, those in functionally relevant regions can significantly alter gene function. Functional changes resulting from SNPs include influencing promoter activity (gene expression) and affecting messenger RNA (mRNA) conformation and stability. This inherited variability is a crucial factor, accounting for ≈ 15 – 30% of inter-individual variability in drug disposition and response, though for certain drugs, this variability can reach up to 95%. The identification and analysis of these variations provide a starting point for developing safer, individualized medication [5, 6].

3.1.2. Genetic Basis of Drug Metabolism: Cytochrome P450 System

The genetic foundation of PGx directly intersects with drug elimination through the Cytochrome P450 (CYP) enzyme system, which functions as the cornerstone of drug metabolism. Genetic factors, specifically the inherited variability in drug-metabolizing enzymes, have a major impact on drug disposition and are responsible for a significant degree of interpatient variability [7]. Variations closely linked to drug metabolism are predominantly observed in Phase I metabolism, particularly within the gene polymorphisms of *CYP2C19* and *CYP2D6* [5]. The CYP enzyme system is central to psychiatric PGx because CYP enzymes are recognized as the primary liver enzymes responsible for drug metabolism.

3.1.3. CYP2D6 and CYP2C19 in Antidepressant Metabolism

In the context of antidepressant therapy, polymorphisms in *CYP2D6* and *CYP2C19* are the most clinically relevant pharmacogenes influencing drug disposition and response. These highly polymorphic enzymes are centrally involved in the metabolism of numerous psychiatric drugs, including SSRIs and TCAs [7].

3.1.3.1. CYP2D6 Overview.

CYP2D6 is one of the most extensively studied PGx biomarkers and plays an essential role in antidepressant metabolism, participating in the clearance of roughly 20% of all therapeutic drugs. *CYP2D6* extensively metabolizes

several antidepressants, including paroxetine, fluvoxamine, venlafaxine, and vortioxetine, typically converting the active parent compound into less active metabolites [8, 9, 7].

3.1.3.2. CYP2C19 Overview.

CYP2C19 is highly involved in antidepressant metabolism, alongside *CYP2D6*. It is responsible for metabolizing about 5 – 10% of all drugs. Importantly, it extensively metabolizes several SSRIs, such as citalopram, escitalopram, and sertraline, usually converting them to much less potent metabolites. The antidepressant escitalopram, for instance, is metabolized by *CYP2D6*, *CYP2C19*, and *CYP3A4* [10, 9, 7].

The extensive polymorphism of these two enzymes dictates that individuals possess different metabolic capacities, impacting the clearance, half-life, and plasma concentrations of most antidepressants. Consequently, genetic testing focuses on these two key enzymes to classify a patient's metabolic status and predict pharmacokinetic variability associated with standard dosing [7].

3.1.4. Diagnostic Metabolic Categories

The inherent functional capacity of these CYP enzymes is determined by the patient's unique combination of inherited alleles, or diplotype. PGx testing utilizes this information to categorize individuals into distinct metabolic phenotypes, which act as diagnostic tools to predict the efficacy and safety profile of standard drug dosages [11, 12]. The resulting phenotypes include poor metabolizers (PMs), intermediate metabolizers (IMs), normal metabolizers (NMs), rapid metabolizers (RMs), and ultrarapid metabolizers (UMs) [7]. Tables 1 and 2 summarize the relationship between *CYP2D6/CYP2C19* diplotypes and the resulting metabolic phenotypes. These phenotypes determine whether a patient under- or over-metabolizes a drug, forming the basis for clinical dose adjustments.

3.1.5. Conceptual Summary

The analysis of *CYP2D6* and *CYP2C19* polymorphisms functions as a preemptive diagnostic tool to classify the individual's metabolic phenotype (UM, RM, NM, IM, or PM). This diagnostic classification is critical for predicting drug exposure levels (pharmacokinetics), which then guides clinical decisions regarding optimal drug selection or necessary dosage adjustments for standard maintenance therapy. This helps personalize treatment and move away from ineffective trial-and-error methods [8, 7, 5].

3.2. Application in Therapy

PGx testing translates genomic variation into actionable therapeutic choices, shifting antidepressant therapy away from trial-and-error and toward a model in which mechanism, exposure, and clinical effect are linked in a predictable way. In practice, this means that the patient's metabolic capacity is used as a starting point for drug selection, dose setting, and interpretation of nonresponse.

3.2.1. Guiding Drug Selection

The primary application of PGx in antidepressant therapy is the initial selection of a medication that matches the patient's metabolic profile. This process aims to maximize efficacy while alleviating the risk of adverse drug reactions (ADRs). The CPIC and the DPWG provide guidelines for specific gene-drug pairs, particularly involving *CYP2D6* and *CYP2C19*, and operationalize this by mapping genotype→phenotype→expected serum concentration→likelihood of response or toxicity [8, 15, 13].

Population differences in *CYP2D6* and *CYP2C19* activity illustrate this chain clearly. In regions where functional variants are especially common, a larger proportion of patients may be predisposed to treatment failure when standard prescribing practices are used. For example, *CYP2D6* gene duplications occur in approximately 20–30% of individuals in Ethiopia and Saudi Arabia (see Fig. 1). The mechanism is straightforward: duplicated active alleles increase enzyme abundance; increased enzyme abundance accelerates clearance; accelerated clearance prevents the drug from reaching its expected steady-state concentration [16]. For TCAs such as amitriptyline or nortriptyline, this yields subtherapeutic serum levels and clinical nonresponse despite adherence. In these cases, guidelines recommend choosing an antidepressant that is not primarily metabolized by *CYP2D6* [17]. Similarly, for *CYP2C19* UMs, citalopram and escitalopram are generally discouraged because of the high probability of subtherapeutic exposure and treatment failure [13].

3.2.2. Dosage Adjustment

When a specific antidepressant is deemed necessary regardless of a non-normal metabolic status, PGx testing helps determine precise dosage adjustments to maintain safety and efficacy. Standard dosing is typically derived from population averages, which may be dangerous for PMs or ineffective for UMs. CPIC guidelines offer specific dosing protocols based on genotype-predicted phenotypes:

- SSRIs: For *CYP2C19* PMs, CPIC recommends a 50% reduction in the starting dose of citalopram, escitalopram, or sertraline [8]. This reduction prevents the accumulation of the drug in the bloodstream, which could lead to dose-dependent side effects such as QT-interval prolongation or serotonin syndrome [13, 18].
- TCAs: For *CYP2D6* PMs, a dose reduction of up to 50% is recommended for drugs like paroxetine and most TCAs to avoid toxicity. Similarly, IMs may require a moderate dose reduction (e.g., 25%) to balance efficacy and tolerability [14].

These adjustments allow clinicians to achieve steady-state drug concentrations that fall within the therapeutic window, thereby reducing the time patients spend on ineffective or toxic regimens [19].

Table 1: Assignment of predicted *CYP2D6* phenotypes based on diplotypes

| Phenotype | Activity score | Genotypes | Example diplotypes |
|--|-------------------------|---|---|
| <i>CYP2D6</i> Ultrarapid metabolizer | > 2.25 | Carries duplications of functional alleles | (*1/*1)×N, (*1/*2)×N, (*2/*2)×N |
| <i>CYP2D6</i> Normal metabolizer | $1.25 \leq x \leq 2.25$ | Allele combinations yielding an activity score of 1.0–2.0 | *1/*1, *1/*2, *2/*2, *1/*9, *1/*41, *41/*41, *1/*5, *1/*4 |
| <i>CYP2D6</i> Intermediate metabolizer | $0 < x < 1.25$ | One decreased-function allele and one no-function allele | *4/*41, *5/*9, *4/*10 |
| <i>CYP2D6</i> Poor metabolizer | 0 | Carries only no-function alleles | *4/*4, (*4/*4)×N, *3/*4, *5/*5, *5/*6 |
| <i>CYP2D6</i> Indeterminate | n/a | One or two uncertain or unknown-function alleles | *1/*22, *1/*25, *22/*25 |

Note. Phenotype assignments were synthesized from the DPWG guideline on *CYP2C19* and *CYP2D6* interactions with SSRIs [13], the CPIC Guideline for Selective Serotonin Reuptake Inhibitors (2023) [8], and the CPIC Guideline for Tricyclic Antidepressants (2016) [14].

Table 2: Assignment of predicted *CYP2C19* phenotypes based on diplotypes

| Phenotype | Activity score | Genotypes | Example diplotypes |
|--|----------------|---|-------------------------|
| <i>CYP2C19</i> Ultrarapid metabolizer | n/a | Two increased-function alleles | *17/*17 |
| <i>CYP2C19</i> Rapid metabolizer | n/a | One normal-function and one increased-function allele | *1/*17 |
| <i>CYP2C19</i> Normal metabolizer | n/a | Two normal-function alleles | *1/*1 |
| <i>CYP2C19</i> Likely intermediate metabolizer | n/a | One normal and one decreased-function allele; or one increased and one decreased-function allele; or two decreased-function alleles | *1/*9, *9/*17, *9/*9 |
| <i>CYP2C19</i> Intermediate metabolizer | n/a | One normal and one no-function allele; or one no-function and one increased-function allele | *1/*2, *1/*3, *2/*17 |
| <i>CYP2C19</i> Likely poor metabolizer | n/a | One decreased-function allele and one no-function allele | *2/*9, *3/*9 |
| <i>CYP2C19</i> Poor metabolizer | n/a | Two no-function alleles | *2/*2, *2/*3, *3/*3 |
| <i>CYP2C19</i> Indeterminate | n/a | One or two uncertain-function alleles | *1/*12, *2/*12, *12/*14 |

Note. Phenotype assignments were synthesized from the DPWG guideline on *CYP2C19* and *CYP2D6* interactions with SSRIs [13], the CPIC Guideline for Selective Serotonin Reuptake Inhibitors (2023) [8], and the CPIC Guideline for Tricyclic Antidepressants (2016) [14].

3.2.3. Treatment of Resistant Cases

PGx is a critical tool for managing Treatment-Resistant Depression (TRD), which is defined as failure to respond to at least two adequate trials of antidepressants [20]. In clinical practice, PGx testing is often reserved for patients who have already failed multiple lines of therapy or experienced severe side effects.

Genetic testing can retrospectively explain treatment failure. For instance, a patient labeled as “treatment-resistant” may actually be a *CYP2D6* UM who never achieved adequate serum levels of the prescribed medication, or a PM who discontinued therapy due to severe intolerance interpreted as non-compliance [21, 22]. Another

clinically important pattern appears in *CYP2D6* PMs taking nortriptyline, where normal doses can drive serum concentrations into the toxic range, leading to anticholinergic side effects, arrhythmia risk, and premature discontinuation that may be misinterpreted as nonresponse [23]. Studies indicate that PGx-guided treatment in patients with MDD significantly improves response and remission rates compared to treatment-as-usual [24, 25, 26]. By identifying the biological drivers of poor response, clinicians can switch to drugs with different metabolic pathways or mechanisms of action, thus overcoming the barrier of resistance.

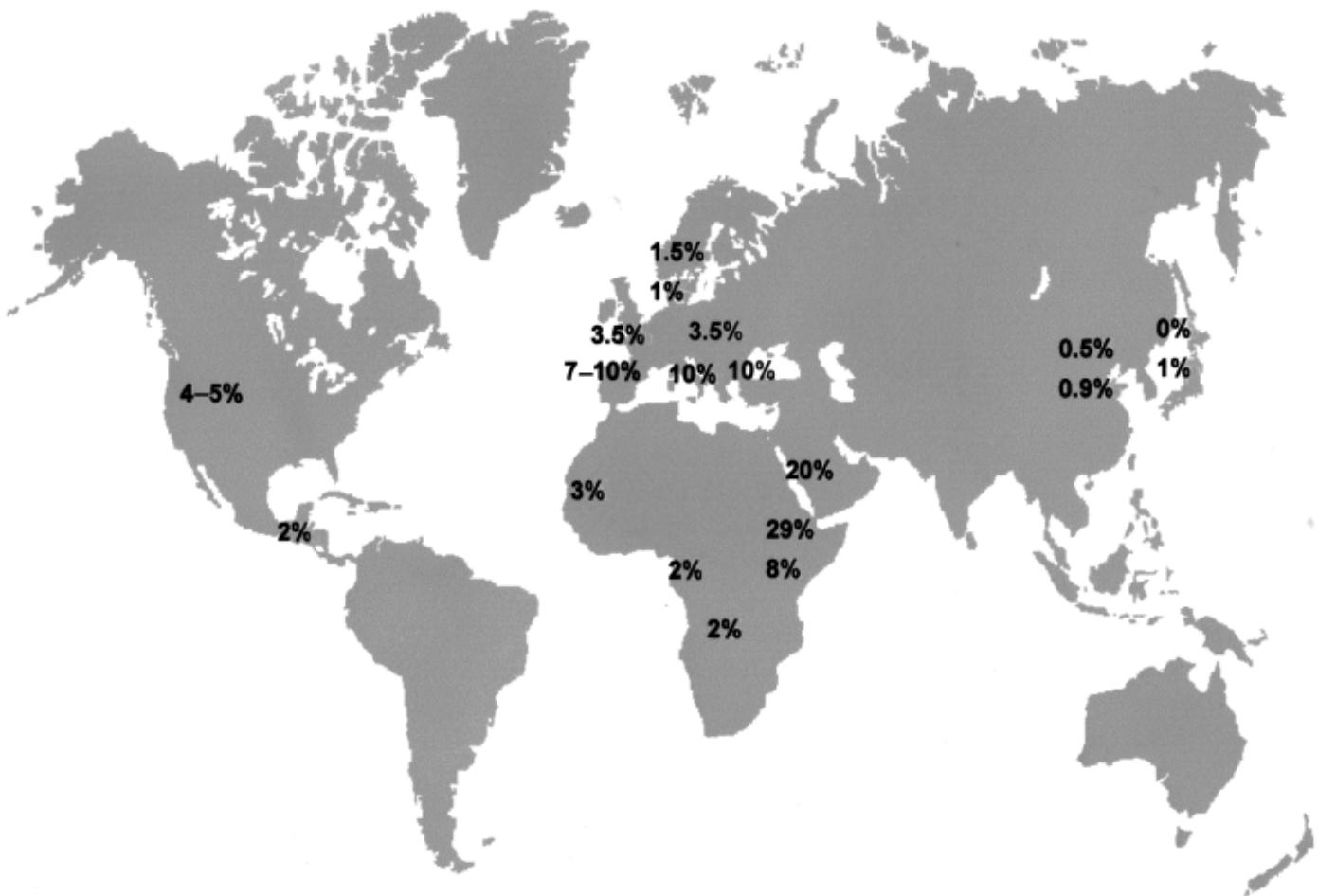


Fig. 1: Interethnic distribution of alleles containing duplicated active *CYP2D6* genes. Reproduced from Ingelman-Sundberg M [2].

3.3. Clinical Challenges and Future Directions

3.3.1. Challenges

High costs of PGx testing represent a primary barrier to implementation in antidepressant therapy, with multi-gene panels often exceeding affordable thresholds in resource-limited settings and lacking consistent reimbursement from insurers [27]. Physician training remains a significant barrier. Many clinicians report inadequate preparation for interpreting PGx results or applying them in prescribing decisions, which limits adoption despite the existence of guidelines [28]. The complexity of multi-gene interpretation further complicates use, since antidepressant response involves interacting variants in genes like *CYP2D6* and *CYP2C19*, where phenotypes such as UMs or PMs require nuanced assessment amid variable evidence strength [29]. Additional obstacles include workflow disruptions, inconsistent clinical guidelines, and data privacy issues that hinder routine PGx application [30].

3.3.2. Future Directions

Future directions in PGx for antidepressant therapy aim to resolve key clinical challenges, such as interpretation complexity, physician education deficits, and workflow inefficiencies, through technological and analytical advance-

ments. Integration of PGx data into Electronic Health Records (EHRs) enables automated clinical decision support [31]. For instance, an EHR system can scan a patient's genotype and flag a *CYP2D6* UM status, prompting clinicians to consider switching to an antidepressant not primarily metabolized by *CYP2D6*; only when alternatives are unsuitable would the system suggest a higher starting dose for agents such as nortriptyline. Polygenic Risk Scores (PRS) will enhance precision by combining multiple loci to predict treatment response, surpassing single-gene limitations and supporting stratified dosing in depression care [32]. Although promising, these scores remain early-stage research tools for antidepressant response, and no clinical guidelines currently support their routine use, so they should be viewed as a longer-term direction rather than an imminent component of standard care [33]. The aforementioned innovations, alongside expanded guidelines and training, promise broader equitable access.

4. Conclusion

This review has demonstrated that PGx testing, particularly focusing on inherited variations in the key drug-

metabolizing enzymes Cytochrome P450 *CYP2D6* and *CYP2C19*, is an essential strategy for improving how we prescribe antidepressants for MDDs. Our main conclusion—that PGx testing can markedly improve the prediction of how a patient will respond to medication—is strongly supported by its established role in clinical practice.

The significant genetic differences found within *CYP2D6* and *CYP2C19* directly lead to distinct metabolic profiles in patients (for example, poor, intermediate, and ultrarapid metabolizers). These profiles, in turn, critically affect the actual amount of an antidepressant (like SSRIs and TCAs) that reaches the bloodstream. To address this, organizations such as the CPIC and the DPWG have developed guidelines that turn this genetic data into practical advice for choosing the right drug or adjusting its dose. This systematic approach allows clinicians to move beyond the traditional, often frustrating, trial-and-error method. For PMs, this means significantly reducing the risk of ADRs; for UMs, it helps ensure the drug is not cleared too quickly, leading to nonresponse. Importantly, PGx testing also provides a valuable tool for addressing TRD, helping clinicians identify biological reasons for non-response and guiding more effective alternative therapies.

Despite the clear benefits, certain roadblocks remain today. These hurdles include the substantial expense of testing, the need for improved training for medical professionals in interpreting these results, and the difficulty inherent in analyzing multiple genes whose effects interact. Nonetheless, the outlook for the future is quite encouraging. We anticipate a smoother, automated process as PGx results are integrated directly into Electronic Health Records (EHRs). Furthermore, the creation of more advanced PRS is expected to make tailored depression treatment both more successful and more widely available to patients. The key takeaway is this: testing for *CYP2D6* and *CYP2C19* is no longer a developing theory; it is now a proven, reliable clinical tool. It offers the most direct and practical path to genuinely individualize antidepressant therapy, which is the most critical factor for enhancing patient results.

5. Author Contributions

- Tran Quoc Hoang: Conceived the study and developed the overall methodology (Conceptualization, Methodology). Managed the project and compiled the manuscript in Quarto (Project Administration, Software). Performed literature synthesis and wrote *Section 3.2 “Application in Therapy”* (Investigation, Writing – Original Draft). Contributed to reviewing and editing the manuscript (Writing – Review & Editing).
- Nguyen Hoang Thanh Ngan: Conducted literature review and synthesized evidence for *Section 3.1 “Genet-*

ics in Etiology and Diagnosis” (Investigation, Writing – Original Draft). Contributed to reviewing and editing the manuscript (Writing – Review & Editing).

- Pham Gia Han: Collected and analyzed background information for *Section 1 “Introduction”* and *Section 2 “Materials & Methods”* (Investigation, Methodology). Wrote these sections (Writing – Original Draft) and contributed to reviewing and editing the manuscript (Writing – Review & Editing).
- Pham Ngo Phuong Thao: Investigated and summarized clinical challenges and future directions for *Section 3.3 “Clinical Challenges and Future Directions”* (Investigation, Writing – Original Draft). Contributed to reviewing and editing the manuscript (Writing – Review & Editing).
- Nguyen Hoang Tuong Vy: Summarized the manuscript to prepare presentation slides (Data Curation, Visualization). Contributed to reviewing and editing the manuscript (Writing – Review & Editing).
- Nguyen Le Ngoc Vy: Summarized the manuscript to prepare presentation slides (Data Curation, Visualization). Contributed to reviewing and editing the manuscript (Writing – Review & Editing).

6. Declaration of Competing Interest

The authors declare no competing interests.

7. Abbreviations

| Abbreviation | Full Term |
|--------------|---|
| ADR | Adverse Drug Reaction |
| CPIC | Clinical Pharmacogenetics Implementation Consortium |
| DPWG | Dutch Pharmacogenetics Working Group |
| EHR | Electronic Health Record |
| IM | Intermediate Metabolizer |
| MDD | Major Depressive Disorder |
| PGx | Pharmacogenomic |
| PM | Poor Metabolizer |
| PRS | Polygenic Risk Scores |
| SSRI | Selective Serotonin Reuptake Inhibitor |
| TCA | Tricyclic Antidepressant |
| TRD | Treatment-Resistant Depression |
| UM | Ultrarapid Metabolizer |

8. Data/Code Availability

The Quarto project underlying this paper—including the manuscript, figures, and bibliography—is available at <https://github.com/ht2905/pgx-antidepressant-response-article>.

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